

1 and the other question. Since there are factors
2 that can influence someone's subjective feelings of
3 sleepiness, do you have any objective measures that
4 support the indication of daytime sleepiness?

5 Specifically, the one trial that I am aware of that
6 had an MSLT and did daytime sleepiness as a primary
7 outcome measure, in fact, appears to be not
8 supportive of the indication.

9 DR. HOUGHTON: Yes, in the Scrima trial he
10 used the MSLT measure and that was not
11 statistically significant, as shown. The objective
12 data that we propose supports very strongly the
13 effect of adequate dosing of GHB was the SXB-20
14 trial that Dr. Black discussed. That is not only a
15 profound improvement in the MWT at the 9 g dose but
16 a defined dose response across all doses. That is
17 very positive data.

18 DR. KAWAS: In ten patients, it appears.

19 DR. HOUGHTON: Twenty-one.

20 DR. MANI: May I also add that that was an
21 open-label, non-randomized study?

22 DR. HOUGHTON: Sure, but using an
23 objective measure.

24 DR. RISTANOVIC: I am I am Ruzica
25 Ristanovic, medical director of Sleep Disorders

1 Center, in Evanston, Illinois. I would like to
2 comment on add-on Xyrem in the presence of other
3 stimulants. Other studies attempt to try to
4 document the effectiveness of other stimulants in
5 narcolepsy-related sleepiness documents, including
6 the most rigorous trial of modafinil in
7 double-blind, placebo-controlled studies. They
8 document that these drugs improve sleepiness but
9 very seldom outside of the range of pathological
10 sleepiness as measured by Multiple Sleep Latency
11 Test and Maintenance Wakefulness Test. So, the
12 patients remain sleepy. That is the message.
13 Add-on treatments are approved for other
14 indications in other neurological diseases, such as
15 epilepsy. So, I assume that this application for
16 that particular indication is not for monotherapy
17 but as an add-on to concurrent use of stimulants.
18 I would like to bring this to your attention. So,
19 patients do remain sleepy on stimulants and they
20 need additional treatments.

21 DR. KAWAS: Dr. Temple?

22 DR. TEMPLE: Dr. Houghton also seemed to
23 be distinguishing between monotherapy and add-on
24 therapy. That is not the problem. The problem is
25 whether there is adequate support for use as an

1 addition for whatever else the patient is on, and
2 whether there are well-controlled studies that
3 support that. So, add-on would be perfectly fine.
4 That is usually true in a lot of conditions, not
5 just neurological ones, where you continue to give
6 standard therapy and try to improve it.

7 I just want to make one observation about
8 the evidence. We do expect to see replicated or
9 reproduced findings. Some of the issues here are
10 whether the fact that the endpoints are secondary
11 and need some correction means that there isn't
12 adequate support. A lot of these things are
13 matters of judgment that the committee can weigh in
14 on. Not everything is, you know, a yes/no. Some
15 of the things are moderately subtle and that is why
16 this is being brought to you for judgment. There
17 is one study that is obviously stronger than the
18 rest but the others can be considered, and you sort
19 of have to think about how many real endpoints
20 there really are; how much of a correction is
21 needed. Those are difficult discussions but worth
22 considering.

23 DR. KAWAS: Dr. Katz?

24 DR. KATZ: I agree, but I think we would
25 still have to have the application meet the

1 standard of independent replication, in other words
2 two trials. You can decide that one of the other
3 trials actually does meet the usual standard,
4 again, taking into consideration the multiplicity
5 and that sort of thing. All I am saying is that I
6 don't think we can say we have one study that looks
7 good. If you believe that GHB looks good and the
8 others sort of contribute to a feeling that it
9 probably is okay, I mean, we really need two
10 independent sources that you believe demonstrate
11 the effectiveness.

12 The only other point I wanted to add is to
13 something, Claudia, you said which has to do with
14 Dr. Houghton's view that they are not going for a
15 claim of daytime sleepiness; they just want, I
16 guess, to have language in the labeling that says
17 that it improves that symptom. Most of the drugs
18 we approve are for symptomatic claims, so there is
19 no question that the inclusion of this language in
20 the indication is a claim as we always understand
21 that term.

22 DR. KAWAS: Dr. Guilleminault, followed by
23 Dr. Wolinsky, please.

24 DR. GUILLEMINAULT: If you look at all the
25 published data on modafinil, on amphetamine, on

1 methylphenidate, none of these drugs ever
2 normalized all the objective tests on alertness and
3 daytime sleepiness. None of them, including the
4 modafinil data which were approved by the FDA. The
5 MSLT and MWT for all these drugs are pitiful. The
6 only data which shows significance was the Epworth
7 Sleepiness Scale, which is a subjective scale, in
8 all these trials. So, we cannot expect to have any
9 positive result with subjective tests in any of
10 these drugs. We will always have to rely on
11 subjective tests even if the subjective test is not
12 great. Everybody in the field agrees that the
13 Epworth Sleepiness Scale is the most used scale
14 despite the fact that it has a lot of downfall, and
15 we have to remember that when we look at what has
16 been approved and what is being used.

17 DR. KAWAS: Thank you, Dr. Guilleminault.
18 I think that many people would agree with those
19 comments, but my question to you would be not
20 whether or not the Epworth Scale subjective
21 measurements are good but do we have two
22 randomized, controlled trials that show an
23 improvement in subjective sleepiness.

24 DR. GUILLEMINAULT: That was my initial
25 question because my understanding is, when the

1 statistician from the FDA responded, she said that
2 when she did a nonparametric analysis she found out
3 that she had a p value of 0.03. So, my
4 understanding is that she had a significant finding
5 even when she did the reanalysis. That was my
6 understanding of her response.

7 DR. KAWAS: Would you like to comment, Dr.
8 Yan?

9 DR. YAN: I am sorry, the previous number
10 is not right. I checked. The number for the
11 nonparametric analysis, the p value was 0.0109.

12 DR. WOLINSKY: I have a couple of
13 questions first for some information before I ask
14 the real question. For the informational questions
15 perhaps Dr. Mignot could help with. So, the first
16 question I have is if you could enlighten us or
17 re-enlighten us about how many patients that have
18 narcolepsy have had cataplexy as a component
19 symptom. What proportion?

20 DR. MIGNOT: In most case series it is
21 about 70 percent.

22 DR. WOLINSKY: The second question is that
23 at least for most of these studies which were done
24 and presented to us since cataplexy was being
25 measured, as is appropriate, the number of

1 cataplectic attacks was relatively high. I think
2 in these studies it was around 20 cataplectic
3 attacks per week. So, how many of the 70, 75
4 percent of patients with narcolepsy who have
5 cataplexy have cataplectic attacks at that level?

6 DR. MIGNOT: I would guess 20 percent.

7 DR. WOLINSKY: Thank you very much.

8 DR. MIGNOT: Yes, roughly.

9 DR. WOLINSKY: And then they would fall
10 down below that level for the remainder of the 55
11 percent of narcoleptics with cataplectic attacks.

12 DR. MIGNOT: If you analyze the spread of
13 the number of cataplexy episodes per week, but you
14 have to balance that also with the efficacy of
15 current treatments. A lot of people that currently
16 have cataplexy that is relatively mild just don't
17 want to take the antidepressants because they have
18 so many side effects, especially sexual side
19 effects, dry mouth, all these problems --

20 DR. WOLINSKY: This is not the question
21 though. So, now the question to Orphan which has
22 really, truly become an orphan drug question, is
23 since all of the studies that have been done have
24 enriched for cataplexy, do we have any data that
25 would suggest that if cataplexy is adequately

1 controlled or if there is no cataplexy so we don't
2 have to worry about the control of cataplexy there
3 would be any effect of the drug on daytime
4 sleepiness in non-cataplectic narcoleptics?

5 DR. REARDAN: I think Jed Black wants to
6 make a comment on that.

7 DR. BLACK: Just a comment on the
8 prevalence of cataplexy in the 70-75 percent of
9 folks with narcolepsy that had cataplexy, the
10 frequency of events -- this is something that Dr.
11 Mignot is not aware of, the cataplexy was
12 subdivided into major events and minor events.
13 About 20 percent or so would have the major events
14 to that level, but when we look at the minor events
15 a far greater percentage of that 70 percent, which
16 may be up to 80, 90 percent of that 70 percent,
17 will have that number of minor effects. Those are
18 not complete attacks where they fall down. In
19 fact, with most narcoleptic patients, they
20 distinguish between the two and they will often
21 only report to the physician the major events. But
22 in the diaries that Orphan had set up all the
23 events are characterized.

24 DR. WOLINSKY: So, the second question --

25 DR. BLACK: We have no idea. That is an

1 excellent question that I think needs to be
2 determined, but in the studies that have been
3 completed that question cannot be answered.

4 DR. REARDAN: Jed, the only study I can
5 think of maybe is SXB-20 where cataplexy was not an
6 entry criterion and I don't know what the cataplexy
7 incidence in that trial was. Bill is shaking his
8 head -- we didn't record it and we didn't
9 quantitate it.

10 DR. BLACK: We can't comment on that.

11 DR. REARDAN: It is true that in most of
12 our studies patients were selected because at entry
13 criteria they had to have a baseline cataplexy.

14 DR. KAWAS: Dr. Penix?

15 DR. PENIX: Before we address the two
16 separate indications issue -- and I guess, Dr.
17 Black, I could direct this question to you -- in
18 the GHB-2 study you did look at all cataplexy
19 events, I guess, and then total and partial
20 cataplexy. In the background material, in the
21 separation of the two it appeared that there was no
22 significant difference in any of the three doses of
23 GHB on total or complete cataplexy but your effect
24 was primarily in partial cataplexy. Is that
25 correct?

1 [No verbal response]

2 So, my question in that regard is what is
3 the clinical significance of partial cataplexy, and
4 you mentioned that patients frequently do not want
5 treatment for partial cataplexy. So, is this a big
6 problem? I presume that the patients that would
7 perceive a problem would be the ones with the
8 complete cataplexy but there we see no significant
9 difference. So, is there a problem there with
10 that?

11 DR. BLACK: I think this is a good point,
12 and the difficulty comes in trying to separate the
13 two because it is not sort of a box of partial and
14 a box of complete; it is a gradation, you know,
15 ranging from small partials to large partials and
16 the completes. So, I think this analysis is
17 difficult to perform. Clinically the degree of
18 improvement with traditional antiepileptic
19 medications that we use is similar. So, the
20 reduction in partial -- if that is all that is
21 being seen here and I am not convinced that
22 clinically that is the case -- while the
23 statistical analysis didn't demonstrate a
24 significant difference in the complete cataplexy
25 attacks, clinically there is an improvement in all

1 the different categories, and it is very
2 substantial in traditional antiepileptic
3 medications as well as with GHB.

4 DR. PENIX: Could Dr. Mignot comment on
5 the clinical significance of partial cataplexy? Is
6 it a big problem?

7 DR. MIGNOT: Yes, it is a big problem. In
8 fact, the problem is especially the social aspect
9 of cataplexy, when you have to realize that you are
10 just in the middle of a crowd and are meeting some
11 friends, and you can never tell when it is going to
12 happen. It may happen in very odd circumstances.
13 So, often even the doctors don't know what it is
14 and they just look at it and they wonder why this
15 person is kind of losing slight control and has to
16 sit down. There is also almost a social aspect
17 with fear of cataplexy that can occur at any time,
18 any moment and, yes, it is a very significant
19 problem.

20 Again, it is a balancing act because the
21 drugs that we use are somewhat effective but they
22 have all these side effects and you just have to
23 choose between two evils. I am pretty sure that,
24 for example, GHB, based on my relatively limited
25 experience, has less side effects than

1 anticataplectic classical tricyclic
2 antidepressants, and that a lot of patients would
3 prefer to take GHB even for partial cataplexy.

4 DR. PENIX: The case that you showed of
5 the nine-year child I assume is complete cataplexy
6 --

7 DR. MIGNOT: Yes.

8 DR. PENIX: -- but you are also saying
9 that patients with partial cataplexy have a
10 significant impairment of their life.

11 DR. MIGNOT: Absolutely. But, as Dr.
12 Black mentioned, it is not an "all or none." I
13 mean, most patients, the ones that are complete,
14 have a lot of partial cataplexy. You never know
15 how bad it is going to be. Most of them are small,
16 little attacks, and sometimes they may even be
17 perceived only by the patient. Sometimes the face
18 may melt; the head drops. Sometimes they just have
19 to sit down; sometimes they don't have to sit down.
20 I showed a young kid because it is more dramatic,
21 but you would see the same thing in some of the
22 patients with partial cataplexy occasionally.

23 DR. BLACK: I am realizing that a
24 definition may be useful here. In general when we
25 were describing patients who documented the partial

1 versus complete, we told them to think about
2 complete as an episode where they fall to the
3 ground with complete paralysis or where, if they
4 weren't sitting, they would have fallen to the
5 ground with complete paralysis. Otherwise,
6 anything else is partial -- so, slurred speech,
7 head drops, dropping things are the partials, and
8 those become very important for quality of life and
9 daytime performance. Driving, those kinds of
10 things can become a very significant event for
11 partials.

12 DR. MIGNOT: Yes, one thing I should also
13 emphasize is that in a very large number of series
14 that, for example, have analyzed several hundred
15 patients with narcolepsy and cataplexy, as a mean
16 the large majority of patients have several attacks
17 per day, several attacks per week. Between several
18 attacks per day and several attacks per week, that
19 is generally partial or complete attacks and it is
20 not something that appears just once, you know,
21 every ten years. It is really something that
22 occurs regularly and sometimes totally
23 unexpectedly.

24 DR. KAWAS: Dr. Falkowski?

25 DR. FALKOWSKI: That leads me to a

1 question just for clarification. For the purposes
2 of these clinical trials, were the cataplectic
3 events something that was just perceived by the
4 patient and recorded in a diary, or were they
5 verified by some third party?

6 DR. REARDAN: These were taken from
7 patient diaries. So, it is patient recorded
8 episodes.

9 DR. HAGAMAN: I am Dr. Hagaman and I just
10 wanted to address the partial versus the complete
11 cataplectic events. I think that you have to take
12 it on an individual basis. We have patients that
13 come in that are teenagers that have tests in front
14 of them and they have a partial cataplectic event
15 and they drop their pencil; people that cut hair
16 that have scissors in their hands and they drop
17 their scissors. So, even though they have not had
18 a complete event, this has been a very debilitating
19 event in their lives. So, it is a continuum and I
20 think you just have to really look at each person
21 as an individual and what they are doing.

22 DR. KAWAS: Dr. Dyer?

23 DR. DYER: How variable in the same
24 patients are the number of cataplectic attacks per
25 week? What is the variance in that?

1 DR. MIGNOT: We have looked at that quite
2 a bit.

3 Actually, I did some diaries in a large number of
4 patients with cataplexy. It is really totally
5 unpredictable and that is one of the most scary
6 parts about cataplexy when you have narcolepsy. Of
7 course, if something emotional is going to happen,
8 say a patient is going to go to a wedding, often
9 they will kind of fear that event much more because
10 they think it is very likely that they are going to
11 have cataplexy in front of everyone and, indeed,
12 they may actually have a lot more cataplexy because
13 it is an emotional event.

14 Still, I have followed, for example,
15 patients and sometimes they may have like 80 for
16 one week and then the following week they may have
17 only three or four. I mean, it can really vary
18 quite a bit. And, one of the main reasons is
19 really that emotion is something that is very
20 variable. In fact, someone mentioned how easy it
21 is to observe cataplexy. It is very difficult to
22 get it on tape because typically the patient come
23 to your office; he really wants to show you what it
24 is but, you know, he is tense and it just will not
25 occur but as soon as he leaves the office and

1 something happens -- boom, he is going to collapse.
2 So, it is very difficult to predict and it is quite
3 variable.

4 DR. ROMAN: For Dr. Mignot also, you
5 mentioned that cataplexy probably is the result of
6 what you called dissociated REM. However, if I
7 recall correctly, the polysomnographic analysis has
8 shown that Xyrem actually decreases the amount of
9 REM sleep and increases delta sleep. Would you
10 like to speculate on what could be the mechanism of
11 action to improve the cataleptic component?

12 DR. MIGNOT: That is a very, very
13 difficult question. One of the difficult
14 questions, of course, is the mode of action of GHB.
15 I have looked into it myself for quite a while
16 because I was trained as a pharmacologist, and it
17 is not clear. There are two camps. Some people
18 think it acts on GHB receptors, specific receptors;
19 others think that it acts through the GABA-B
20 receptors. We know that it has some strong effect
21 on dopamine transmission. If you inject GHB in
22 animals the rate of activity of dopaminergic cells
23 shuts down and dopamine can increase in the brain
24 proportionally to the dose. We have done quite a
25 bit of studies that have shown that the

1 dopaminergic system is very important to regulate
2 both wakefulness and also cataplexy and the
3 regulation of emotion. I believe it is by changing
4 the balance of the dopaminergic system, that
5 improves cataplexy the following day maybe by
6 increasing dopamine in the brain during the night,
7 but this is highly speculative and a lot more
8 research needs to be done.

9 The fact that it does not increase REM --
10 first, it is quite variable because some studies
11 have shown that it does increase REM and this
12 contrasts dramatically with what all hypnotics do.
13 If you take MVN or all the other
14 benzodiazepine-like hypnotics, what they do is
15 actually, rather, reduce slow wave sleep and reduce
16 REM sleep. Xyrem doesn't do that. It actually
17 promotes slow wave sleep and, if anything, would
18 promote REM sleep or doesn't change it. That is
19 still, you know, much more in the right direction
20 of promoting normal sleep, including REM sleep.

21 The last comment I want to mention is that
22 it is not sufficient -- if you know a lot about
23 narcolepsy, it is not sufficient to just explain
24 narcolepsy as a disorder of REM sleep. Indeed,
25 they have all this transition to REM sleep but they

1 also have impaired wakefulness per se. For
2 example, if you do MSLTs they don't always go into
3 REM. They will often just fall asleep into normal
4 sleep. So, it is not only REM sleep that is
5 disregulated in narcolepsy, it is also wakefulness
6 and by improving slow wave sleep you presumably
7 also can improve the wake aspect of narcolepsy. My
8 answer may be a little complicated but I would be
9 happy to discuss it in more detail.

10 DR. KAWAS: Dr. Van Belle?

11 DR. BLACK: Just another comment on that,
12 the Broughton study showed an increase in REM at a
13 lower dose. The first dose of the SXB-20 that I
14 participated in showed at 4.5 g the first night an
15 increase in REM, which was then followed by a
16 dose-related decrease in REM over time, which is
17 very different from REM suppressant agents where
18 there is a robust, or in fact the largest effect
19 that can often be seen on the first night of
20 administration.

21 So, we don't know exactly why it is that
22 over time the REM with higher doses is reduced, and
23 why with the first dose, and with the lower doses,
24 as has been demonstrated here with Roger
25 Broughton's work, why the REM is increased. There

1 has been established sort of a competitive reaction
2 between slow wave sleep and REM sleep. It appears
3 that there may be factors that regulate slow wave
4 sleep that also are important in regulating the
5 appearance, or lack thereof, of REM sleep. It may
6 be that gamma hydroxybutyrate is sort of normalizing
7 slow wave activity which then results in a more
8 normal control or regulation of the REM or
9 REM-related events.

10 DR. KAWAS: Can I ask for my
11 clarification, what dose the company is proposing?

12 DR. REARDAN: Bill, can you take that
13 question?

14 DR. HOUGHTON: Yes, the dosage regimen
15 that we are proposing is that patients be started
16 at 4.5 g and then titrated between the range of 3-9
17 g to clinical efficacy. Although in the strictest
18 mathematical sense the only statistical efficacy in
19 the GHB-2 study was clearly defined at 9 g, that
20 may well represent that the study was too short
21 because in the open-label study that followed, as I
22 showed, the maximum nadir occurred at 8 weeks, and
23 when those patients were followed over the course
24 of 12 months they maintained efficacy across the
25 dose range. Certainly, there is an advantage in

1 terms of the important side effects to dose
2 titration. In all of the treatment IND protocols
3 and the safety studies the data was generated at
4 between 3-9 g. Now, 80 percent of the patients
5 were maintained between 6 g and 9 g, but there was
6 certainly facility for down-titration from the 4.5
7 or maintenance there as well.

8 DR. KAWAS: Thank you. Dr. Van Belle?

9 DR. VAN BELLE: It seems to me that there
10 is reasonable agreement with respect to efficacy
11 for cataplexy at least between the FDA and the
12 sponsor. So, I would like to get back to the
13 secondary endpoints. I would like to ask a
14 question to the sponsor's statistician, Dr. Trout,
15 as to whether he thinks that multiple comparisons
16 is a problem. Secondly, if multiple comparisons
17 are a problem, how he would adjust.

18 DR. REARDAN: Do you want to put this in
19 relation to a specific trial or all the trials in
20 general?

21 DR. VAN BELLE: Well, I bring it up in
22 connection with the analysis of Dr. Mani where he
23 clearly comes to conclusions that differ from yours
24 with respect to the efficacy of some of these
25 secondary endpoints.

1 DR. TROUT: You know, it is hard to answer
2 that question. I think the way I would answer that
3 is as follows: The GHB-2 analysis, the results
4 that we found and also that were expressed earlier
5 were very strong. So, even with the fact that
6 there is some multiplicity, we also have, remember,
7 some other outcome measures which were related to
8 this particular general area in terms of daytime
9 sleep attacks. So, there were at least two
10 measures that suggested improvement with respect to
11 that particular outcome.

12 The other second study that has been
13 discussed is the Lammers study, and that study is
14 obviously much smaller. It is obviously a weaker
15 study, and there is some issue with regard to
16 whether the appropriate method of analysis was
17 there. So, I think that is a harder one to
18 address.

19 Now, there are two kinds of multiplicity
20 going on here, which you are well aware of. One is
21 the multiplicity with regard to the multiple dosing
22 levels and that was accounted for in our analyses.
23 The question that was brought up by Dr. Mani with
24 regard to the multiplicity of secondary endpoints,
25 and I am not a betting man but I think there is

1 certainly evidence to suggest that daytime
2 sleepiness is being affected possibly. But I don't
3 go to Las Vegas nor Atlantic City.

4 DR. KAWAS: Actually, while we have Dr.
5 Trout up, I would ask him with regard to excessive
6 sleepiness on the Epworth Scale in the GHB-2 study,
7 while there certainly was a difference in the two
8 groups, there were also major baseline differences
9 in sleepiness for the responders and the
10 non-responders. In fact, those that appeared to
11 respond had a baseline that was better than the
12 improvement in the other group. There was a
13 significant difference. Are you concerned about
14 these and how these might affect the results?

15 DR. TROUT: There is always concern about
16 baseline differences, and that was attempted to be
17 accounted for in two mechanisms, one, we looked at
18 change from baseline and we also did a covariate
19 adjustment to try to account for that.

20 DR. KAWAS: Dr. Katz?

21 DR. KATZ: I would like to ask Dr. Trout a
22 question also. Dr. Yan mentioned that we didn't
23 believe that the data were normally distributed,
24 and when you transformed the data it didn't really
25 help very much. I don't want to get bogged down in

1 a hyper-arcane discussion about normally
2 distributed data, but when we did that we got a p
3 value for that comparison -- I guess it was the
4 Epworth, of about 0.01 --

5 DR. MANI: I am sorry, it wasn't the
6 Epworth. You are talking about the Lammers study
7 where you are talking about the frequency --

8 DR. KATZ: I thought we were talking about
9 GHB-2.

10 DR. MANI: Oh, sorry, fine.

11 DR. KATZ: So, if we are right, it takes
12 the p value which was 0.0001 or something like that
13 to 0.01, and then when you get to the multiple
14 comparisons issue it makes it less weak. I agree if
15 you take a p value of 0.001 or 0.0001, no matter
16 what you do to it as far as a multiple comparison,
17 it is still going to be significant. But if it is
18 0.01 it is a little different story. So, I am just
19 wondering, again without getting into excruciating
20 details, what about this question of the data being
21 normally distributed and not necessarily being
22 improved very much by transforming it? Is there
23 common agreement about that or not?

24 DR. TROUT: My recollection, and it has
25 been sometime since I have seen the results of the

1 analysis, is that it suggested that we didn't see a
2 particular problem with the normal distribution as,
3 for example, was the case with cataplexy which was
4 clear. I am not sure if Dr. Yan did a
5 nonparametric covariance analysis or not. I
6 haven't seen those analyses. And, I think the
7 point was made earlier that that would be, I think,
8 an appropriate thing to do in order to account for
9 some potential baseline differences. If she did,
10 then whether it is a reflection of a decreased
11 sensitivity of a nonparametric analysis or whether
12 it is a normal distribution -- I can't answer that
13 without seeing the data. Maybe it was just a
14 standard, nonparametric analysis which might help
15 account for the difference.

16 [Comment away from microphone; inaudible]

17 DR. TROUT: No, I know that but Dr. Yan
18 did a nonparametric analysis because she was
19 concerned about the normality, and did look at the
20 log transformation and it didn't have any impact on
21 that, which doesn't surprise me at all.

22 DR. KAWAS: I would like to ask the
23 sponsor, I mean, there clearly was a dose
24 relationship in terms of the adverse events. Were
25 any other factors looked at that may be related to

1 the adverse event profile, things like age, even
2 previous psychiatric history, other medications?
3 Whether or not they drank alcohol? Anything?

4 DR. HOUGHTON: No, we didn't go as far as
5 an alcohol history. Certainly for the major
6 psychiatric, a preexisting history of major
7 psychiatric disease emerged. Major psychiatric
8 disease was actually a protocol exclusionary
9 criterion, but in those that, for instance
10 attempted suicide, post-study it was discovered
11 that they had a previous psychiatric history and in
12 actual fact in one of the patients a previous
13 suicide attempt had been made. There was major
14 depressive disease reported in those, but for those
15 who developed psychosis there was definite recorded
16 preexisting psychiatric history.

17 In terms of age, we haven't done a
18 breakdown of the database, and in most instances
19 there was not a dose relationship. There were just
20 instances that were mentioned in the presentation.
21 Confusion and sleepwalking suggested a dose
22 relationship. In the GHB-2 protocol which was
23 obviously blinded, there was the association with
24 nausea, vomiting, confusion and enuresis that was
25 definite, but that didn't extend across the whole

1 study database. So, the relationship with dose is
2 not well defined.

3 DR. KAWAS: But how about relationship
4 with anything else? For example, were the patients
5 who had confusion more likely to be the elder
6 patients? You might be able to tell I am in aging.

7 DR. HOUGHTON: I can identify well. Do we
8 have a breakdown of confusion by age? A range
9 would be still useful.

10 [Slide]

11 Here is a slide that shows that the
12 distribution of age was between 25 and 73 years,
13 with 67 percent over 50 years of age, but the range
14 is still wide. There is the distribution across
15 doses. Four events at 3 g, 10 at 4.5, 12 at 6 g, 8
16 events at 7.5, and 13 events at 9 g.

17 DR. KAWAS: Thank you. Do we have any
18 other questions from the committee? If not, we
19 will move on. Dr. Katz?

20 DR. KATZ: A quick question, if I heard
21 you correctly, there were 14 events reported as
22 convulsions, but when you went back and looked at
23 that, 13 of them were actually cataplexy. So,
24 presumably cataplexy was a verbatim term. How is
25 it that cataplexy got coded as convulsions?

1 DR. REARDAN: The COSTART dictionary puts
2 cataplexy in as a convulsion. It is a definition.
3 Convulsion has ten different terminologies,
4 verbatim events, and they all code up to
5 convulsion.

6 DR. WOLINSKY: Along those lines, how come
7 there were only that few number of convulsions when
8 we were studying cataplexy in the trial? I mean, I
9 don't know that it is easy to explain this in both
10 sides of one's mouth.

11 DR. HOUGHTON: No, and we are not trying
12 to. If there was a cataplexy event that occurred
13 of a severity to be seen as unusual for that
14 patient, and the patient volunteered it as an
15 event, then it was recorded as an adverse event.
16 Or, there may have been injury related to the
17 cataplexy events. We do have representation in the
18 database. I can recall absolutely a fractured
19 ankle in the washout study. So, there were
20 traumatic events associated with a major cataplexy
21 event that would have been of sufficient impression
22 on the patient to report as a separate event.

23 DR. WOLINSKY: But then the event would
24 not have been withdrawal from the primary measure
25 of efficacy even though it was also registered as

1 an adverse event?

2 DR. HOUGHTON: I am sorry?

3 DR. WOLINSKY: Was it still counted as an
4 event in the measure of efficacy if it was also
5 shifted to be counted as an adverse event?

6 DR. REARDAN: Yes, the patient diaries
7 recorded cataplexy. If they record cataplexy as an
8 event itself, that was part of the efficacy
9 outcome. It wasn't necessarily an adverse event.
10 If they had an adverse event -- fall and break an
11 ankle, cataplexy is coded as part of that adverse
12 event. It is the cause of the adverse event and so
13 it shows up in the database.

14 DR. KAWAS: Dr. Simpson?

15 DR. SIMPSON: I have two questions. One
16 really was just a clarification of this business
17 about the sleepiness. I think we have all agreed
18 that there has to be some adjustment for multiple
19 comparisons on the sleepiness index, and the GHB-2
20 study, even if you make an adjustment, there are
21 certainly some of the indices about sleepiness
22 which seem to be significant. But coming back to
23 the Lammers study, have we established whether or
24 not, once we have made an adjustment, we have any
25 significance there or not? Because that is the

1 pivotal trial, isn't it, because we need two?

2 DR. REARDAN: Remember that the Lammers
3 study was a very small trial, 24 patients. Daytime
4 sleepiness was a secondary endpoint in that study,
5 and I forget the p value. Maybe Dr. Yan or Dr.
6 Katz could comment. I don't think any formal study
7 of multiple analysis was done, except maybe by Dr.
8 Yan --

9 DR. YAN: No.

10 DR. REARDAN: -- and I think she needs to
11 comment on that.

12 DR. YAN: For Lammers study there was no
13 prespecified analysis, except the Wilcoxon assigned
14 rank test. It was across the study and we
15 considered it not very appropriate, and for a
16 secondary analysis none of the statistical analyses
17 were specified. The problem with this Lammers
18 study is that if you use different statistical
19 analyses which are considered appropriate, you get
20 a very different result. Some could be less than
21 0.05 and some ranged to something like 0.2. So,
22 the results are not consistent and we don't have a
23 reliable method to see which one we could consider.

24 DR. REARDAN: We don't disagree with that.
25 I mean, the problem with Lammers is that it was a

1 one-sentence statement about how he was going to
2 analyze it, and it was an inappropriate statistical
3 analysis for a crossover study. So, that creates
4 issues about not having a prospective statistical
5 plan appropriate for the study. But even in that
6 initial Wilcoxon analysis the daytime sleepiness
7 was statistically significant. It was not
8 corrected for multiple analyses.

9 DR. KAWAS: Dr. Simpson?

10 DR. SIMPSON: I just have another question
11 that I wondered if you could clarify. In a lot of
12 these studies you talk about an intent-to-treat
13 analysis, but when I read it I wasn't clear whether
14 or not that meant the patients that were randomized
15 were actually included always in the analysis or
16 not.

17 DR. REARDAN: Yes, the intent-to-treat
18 would include every patient who received drug. Is
19 that correct?

20 DR. TROUT: Yes, every patient who
21 received at least one dose.

22 DR. SIMPSON: So, how did you then deal
23 with the patients who dropped out?

24 DR. TROUT: In the GHB-2 analysis we
25 selected an endpoint. So, in order for the patient

1 to be included in that analysis there had to be at
2 least one post-baseline measure of cataplexy or
3 sleepiness, or whichever outcome you want. So, it
4 was an endpoint analysis that was done in order to
5 accommodate that.

6 DR. KAWAS: It looks like we are
7 completely behind schedule and we will have a very
8 late lunch, I will warn everyone. The FDA's
9 invited speakers on risk management issues is the
10 next component of this discussion. The first
11 speaker is going to be Dr. Carol Falkowski, of the
12 Hazelden Foundation, in Minnesota, who will be
13 speaking on the epidemiology of GHB abuse issues.

14 FDA Invited Speakers on Risk Management Issues
15 Epidemiology of GHB Abuse Issues

16 DR. FALKOWSKI: Hello. Good morning,
17 almost afternoon.

18 [Slide]

19 This is the title of my talk, GHB Abuse in
20 the United States. I am Director of Research
21 Communications at the Hazelden Foundation. I have
22 been a member of the National Institute on Drug
23 Abuse's Community Epidemiology Work Group since
24 1986. I am author of a book, called, "Dangerous
25 Drugs: An Easy-to-Use Reference for Parents and

1 Professionals." What is missing from this overhead
2 is that I served on the Drug Abuse Advisory
3 Committee for the FDA from 1995 through 1999.

4 [Slide]

5 In the very short time that I have, I am
6 going to try and just hit the big points about what
7 we know about the abuse of GHB in the United
8 States, starting off with measuring drug abuse.
9 There are a number of things that are thought to
10 bear when we talk about measuring something as
11 complex and multi-dimensional as drug abuse. This
12 includes population surveys. It includes hospital
13 emergency room episodes; medical examiner data;
14 addiction treatment data; law enforcement data, as
15 well as ethnographic studies that look at specific
16 populations of users that are more anthropological
17 and ethnographic in nature.

18 [Slide]

19 I also want to make the point that all
20 data systems have limitations, and this is
21 particularly true in the case of new drugs of
22 abuse. For example, if we are talking about GHB
23 and trying to measure the number of patients who
24 have presented to addiction treatment centers
25 across the country with GHB as their primary drug

1 of abuse, it is now the case that it is often
2 grouped in a category of drugs called sedative
3 hypnotics. It is not its own line item. So, in
4 preparation for a meeting like this it is very hard
5 to get an accurate count of the extent to which GHB
6 itself is the presenting drug of abuse.

7 Similarly, surveys that are conducted --
8 we have not added GHB to the National Household
9 Survey or the Monitoring the Future Survey,
10 although to the Monitoring the Future Survey that
11 looks at drug use among 8th, 10th and 12th graders
12 ecstasy, another club drug, has been added.

13 Also, in terms of law enforcement
14 indicators, there is no field test for GHB so it is
15 hard to also get that indication of it as well.

16 In addition, new methods of abuse are hard
17 to track. I recall, in 1986, when we started at
18 the national level wanting to track crack cocaine,
19 we knew about how to track cocaine but, all of a
20 sudden, we were looking at it by a different route
21 of administration. So, it was a challenge to all
22 of us to start switching our data systems just to
23 measure crack instead of cocaine, to make that
24 distinction.

25 Existing data systems are slow to respond,

1 and there is a system-wide learning curve when a
2 new drug of abuse appears on the scene. That means
3 it is a learning curve in terms of emergency room
4 personnel, treatment providers, law enforcement, as
5 well as prevention agencies, and that is why we
6 rely on a lot of the scientific literature put out,
7 particularly in emergency medicine, to inform the
8 field about emerging drugs of abuse and how people
9 present with those problems.

10 [Slide]

11 My background in this has been as part of
12 the Community Epidemiology Work Group. This is a
13 group of drug abuse researchers from twenty cities
14 in the country that has been convened by the
15 National Institute on Drug Abuse since 1976. This
16 model of drug abuse epidemiology has also been
17 adapted in different parts of the world. There is
18 a similar group in Europe, in Canada, Mexico and
19 Asian cities.

20 [Slide]

21 The Community Epidemiology Work Group is
22 an early warning epidemiological surveillance
23 network that detects new drugs of abuse, patterns
24 of use and populations at risk.

25 [Slide]

1 It involves researchers looking at the
2 same data from different geographic areas and in
3 this case, as I mentioned, there are people like me
4 in twenty cities in the country who write
5 quantitative reports on drug abuse twice annually,
6 and we are convened by the National Institute on
7 Drug Abuse twice a year.

8 [Slide]

9 Having done this and written over twenty
10 reports on drug abuse trends in my city and met
11 with my colleagues, it has given me a sort of
12 broad-based perspective on how emerging drugs are
13 measured and how we get a handle on them. But
14 everyone looks at medical examiner data. We look
15 at the data from the Drug Abuse Warning Network,
16 which is data from a representative sample of nine
17 federal short-stay hospitals with 24-hour emergency
18 rooms, and that is conducted in 21 cities, as well
19 as some other areas of the country.

20 We also look at treatment data, law
21 enforcement data and price, purity, trafficking and
22 the sale of drugs, as well as supplemental research
23 data and information from multiple sources.

24 [Slide]

25 I want to start my introduction to GHB by

1 telling you about the abuse of a group of drugs
2 that are called club drugs. That is really the
3 first time in a long time we have had a name like
4 club drugs applied to drugs because they are used
5 in a particular setting. That is why they came to
6 be called club drugs. It is a mixed category of
7 drugs. It includes stimulant drugs as well as
8 depressant drugs that are used in nightclub
9 settings. GHB is also known in these settings as
10 liquid X, gamma, G, easy lay, Georgia Home Boy or
11 great hormones at bedtime. MDMA or 3,4 methylene
12 dioxide methamphetamine is ecstasy, e or x.
13 Ketamine is known as special K. It is a veterinary
14 anesthetic, a dissociative drug similar in effects
15 to PCP. Flunitrazepam, Rohypnol is a long-acting
16 benzodiazepine, which was dubbed the original date
17 rape drug which is a drug not approved for medical
18 use in this country; methamphetamine and LSD.

19 If there is one point to make about club
20 drugs as a term, one thing that has emerged is the
21 fact that clearly these drugs are not limited to
22 club settings and I will be talking to that in a
23 moment. It is not just clubs where they are used.

24 [Slide]

25 To give you a little slice of the

1 progression of GHB and how it came on the CEWG
2 radar screen, it was first mentioned in 1990
3 through a poison information center from my
4 colleague in Miami. Then, from 1990 to 1994 it
5 appeared in the Miami and the New York city
6 reports. In 1996 it appeared in 6 other cities,
7 and by the year 2000 most cities in this 21-city
8 work group were reporting GHB. It reports 23
9 deaths in the 20 CEWG cities, and I refer you to a
10 handout that I prepared that sort of gives the
11 chronology of how my colleagues describe the
12 growing abuse of GHB in their cities.

13 [Slide]

14 Now, in terms of user typologies, they
15 tend to be young adolescents through adulthood.
16 There is really no age group but when we look at
17 population surveys in this country of who are drug
18 abusers, by and large the biggest bulk of drug
19 abusers are people who are under the age of 35.

20 The motive for use is multiple. It
21 includes not only intoxication, but also people
22 seeking intoxication effects in the absence of
23 alcohol. I have had people describe it to me as it
24 gives them the effects of alcohol without having to
25 waste that time drinking alcohol. This is by young

1 people who haven't developed the taste.

2 It is also used by weight lifters and body
3 builders for its alleged anabolic effects. It is
4 also marketed in nutritional supplements to promote
5 better sex, better sleep and some people take it to
6 counter the effects of other club drugs. One of
7 the characteristics of drug abuse in nightclubs
8 that has come up over the past year is the fact
9 that people seem to have the impression that if you
10 take just a little bit of this and a little bit of
11 that nothing can really hurt you in a club setting.
12 So, you might take a little bit of ecstasy to get
13 you going, with a little bit of cocaine to keep you
14 there, and maybe a little bit of heroin to take the
15 edge off. This sort of mixing and matching is also
16 part of the user typology.

17 The settings it is used in are nightclubs,
18 raves, parties, but also in homes, in health clubs,
19 gyms and other settings. The sources of it come
20 from health food stores, mail order kits, the
21 Internet or at these clubs where it is being used
22 by the capful. Sometimes at these clubs, because
23 ecstasy dehydrates you, people have a lot of water
24 bottles and it is not unusual to have a water
25 bottle that may have GHB mixed in it, and for ten

1 bucks someone can get a swig of it. This makes it
2 very imprecise dosing, as you can imagine.

3 [Slide]

4 In terms of deaths, in terms of the
5 consequences of use -- there is a huge bullet
6 missing from this slide, which I will get to. So,
7 if everybody wants to find their slides and write a
8 bullet in it, I would appreciate it. Deaths --
9 there have been 71 documented deaths, according to
10 the Drug Enforcement Administration, through
11 November of last year. Again, the problem is that
12 because it is a new drug of abuse people don't
13 know. You know, you have to know what you are
14 looking for to be able to find something and this
15 has clearly been the case in trying to document GHB
16 deaths. It is a huge issue and I hope we get
17 enlightened on that this afternoon.

18 Also, there have been adverse medical
19 reactions, not only people who come into emergency
20 rooms, but the countless people, which is quite
21 hard to quantify, who have episodes but never get
22 emergency room treatment for it. But there have
23 been medical reactions, adverse ones.

24 Dependence -- there has been a reported
25 increase in people presenting to addiction

1 treatment centers with GHB as their primary
2 substance of abuse, and an increase in the reported
3 addiction to GHB by those who may not make it to
4 treatment programs.

5 I work at the Hazelden Foundation. We are
6 based in Center City, Minnesota, with campuses in
7 Chicago, New York City and West Palm Beach. There
8 were 5 patients in 1999 who had a history of GHB
9 abuse, and that had grown to 39 in the year 2000
10 and we are just one treatment center.

11 Finally, the missing bullet on here is
12 drug rape. One thing we have seen in this country
13 since the early 1990's is the use of drugs, this
14 predatory use of drugs where you administer drugs
15 to people without their knowledge for the purpose
16 of disabling them to commit crime on them. The
17 first drug that came to this sort of notoriety was
18 Rohypnol, but now we are in a situation where GHB
19 is often used in drug-induced rape. In fact,
20 several years ago when President Clinton signed the
21 federal date-rape law, the Samantha Reid and Hilary
22 Farris Date Rape Act, that was in response to two
23 cases of drug rape that were not related to
24 Rohypnol but to GHB. So, that bullet should be up
25 there, drug rape.

1 Also, another bullet would include the
2 trafficking, sale and manufacture, the law
3 enforcement consequences.

4 [Slide]

5 Let's look at hospital emergency room
6 episodes of GHB. This looks at them from 1994
7 through 1999. You can see the increase in hospital
8 emergency department mentions of GHB. Mentions is
9 sort of unusual term for people who aren't familiar
10 with the Drug Abuse Warning Network, and it quite
11 literally means, in a retrospective review of
12 patient records, that they find a mention of GHB.
13 Sometimes it is the sole drug that precipitated the
14 medical emergency and sometimes it is used in
15 combination with other drugs. For every drug abuse
16 episode in the Drug Abuse Warning Network there can
17 be the mention of 4 drugs and alcohol, but when
18 alcohol is used in combination with other drugs; it
19 is not an alcohol tracking system.

20 [Slide]

21 So, this is what it looks like through
22 1999. This looks at it by half year increments.
23 You can see this takes us into the year 2000 and we
24 have the first half of the year 2000.

25 I want to go back to just my opening

1 remarks about club drug abuse. I think in the
2 general population when we think of club drugs, you
3 know, what we hear about, what everybody is talking
4 about, what seems to be in U.S. News and World
5 Report, in Newsweek and Time Magazine is ecstasy.

6 [Slide]

7 This is from exactly one year ago. This
8 is Time Magazine from June 5, 2000. It talks about
9 ecstasy. For many folks, club drugs -- you think
10 ecstasy.

11 [Slide]

12 This was, I believe, from Time magazine as
13 well. You see the water bottle there. If you
14 didn't see Time magazine, you may have seen The New
15 York Times Sunday magazine insert. This is from
16 January of this year, talking again about ecstasy.
17 This is from January 2001.

18 So, since it is in the same category of
19 drug, I think it is relevant to look at how GHB
20 emergency room episodes compare with those of
21 ecstasy.

22 [Slide]

23 Ecstasy, or MDMA, is in the pink and GHB
24 is in blue. You can see in the first half of the
25 year 2000 that GHB hospital emergency episodes have

1 surpassed those of ecstasy.

2 [Slide]

3 Efforts to control GHB -- a number of
4 states have done things to try to control GHB abuse
5 in their states. This is sort of a listing of the
6 scheduling of it in various different states. It
7 was added, as you know from the materials the
8 committee received, to the Federal Control
9 Substance Act.

10 [Slide]

11 Finally in conclusion, GHB is a
12 significant, growing drug of abuse. We have seen
13 rapid growth in the adverse medical consequences
14 related to GHB since 1999 and, in fact, hospital
15 emergency mentions of GHB now surpass those of
16 ecstasy or MDMA. We have seen rapid growth in
17 adverse medical reactions despite not only federal
18 scheduling but the scheduling in numerous states.
19 We have multiple user typologies. This is not a
20 substance that is sought after simply by people at
21 parties and raves. These products that contain GHB
22 as well as its precursor drugs, GBL and 1,4-BD, are
23 sought after by people who believe the claims on
24 these nutritional supplements and take them for
25 promoting muscle growth, for sleep; and take them

1 for better sex, as well, and as I said, use it in
2 sort of predatory way. Dependence is clearly
3 possible.

4 So in closing, here we have a drug with an
5 established widespread abuse record. With GHB we
6 needn't talk about abuse potential. With GHB we
7 have abuse reality. We have a decade of GHB abuse
8 in this country; a decade of deaths and hospital
9 emergency room episodes and dependence. We have
10 escalating abuse of GHB in spite of recent efforts
11 to control it and, yes, people acquire this drug
12 and its precursors in many ways. But make no
13 mistake, the effects being sought are the GHB
14 effects. The chemical agent in the body that is
15 producing these effects is GHB, and this
16 undisputable fact is entirely relevant to our
17 discussions today.

18 I have to take issue with the statement
19 from the sponsor that says Xyrem is not the
20 problem. If Xyrem equals GHB, then I believe it is
21 a problem. This drug, if approved, will exist
22 outside the confines of this room. Patients will
23 use it outside the confines of clinical trials. In
24 America, in 2001 we have a serious, significant and
25 growing problem with GHB abuse in this country, and

1 it just so happens that this coincides with Orphan
2 Medical seeking approval for this drug.

3 This drug already has avid followers, and
4 there is no reason to assume that another source of
5 GHB would not be sought after by these folks, and I
6 think we need to bear that in mind throughout our
7 discussions. Thank you.

8 DR. KAWAS: Dr. Falkowski, can I ask you
9 one question? With regards to the emergency
10 department data for GHB, I recognize the
11 difficulties of all of this kind of data but, for
12 example, MDMA is not infrequently the only drug and
13 when they go to the emergency room that is clearly
14 because of the MDMA. Can you give us any kind of
15 quantification or semi-quantification? You
16 mentioned that sometimes GHB is the only drug.

17 DR. FALKOWSKI: The question was how often
18 is GHB used in combination, and let me find that.

19 DR. KAWAS: For the emergency room data.

20 DR. FALKOWSKI: Yes, that is what I am
21 looking for. I have it right here. It is 70
22 percent of the time. Like many other drugs, GHB
23 episodes involve drugs other than GHB as well.

24 I would also like to add that I believe
25 these hospital emergency room episodes

1 underestimate GHB because drugs that are used in a
2 predatory way, that are administered to people
3 without their knowledge are not DAWN reportable.
4 So, if someone comes to the emergency room and says
5 I believe somebody gave me something and it is
6 making me sick, that is not a DAWN reportable
7 thing. That is being addressed by the Substance
8 Abuse and Mental Health Services Administration.
9 But what that means is that people who are drugged
10 with any sort of drug are not picked up by this
11 particular reporting system.

12 DR. KAWAS: And, what are the most common
13 drugs or classes of drugs that go along with GHB
14 when people take them in combination? What are the
15 favorites?

16 DR. FALKOWSKI: It is probably ecstasy,
17 MDMA, and to a lesser extent ketamine and also
18 alcohol.

19 DR. SANNERUD: I have some data on the
20 DAWN statistics too. When drugs are used in
21 combination, 50 percent alcohol, 11 percent
22 stimulants, 8 percent marijuana, poly drugs,
23 hallucinogens and sedatives and all these are at
24 least at 3 and 2 percent each.

25 DR. KAWAS: Dr. Dyer, I believe you are

1 our next speaker.

2 DR. KATZ: Claudia, if I could just ask a
3 question, and I don't know who best to direct it,
4 but you said 70 percent of the time the reports are
5 of GHB in association with something else. So,
6 presumably 30 percent of the time it is the sole
7 drug. I have a sort of methodologic question. How
8 reliable would you say that information is, just in
9 general? What is sort of the nature of the
10 information that is recorded and from whom that
11 allows us to conclude that, in fact, GHB is the
12 only drug that was taken? Who reports that, and
13 how reliable are those reports, just as a general
14 rule? Number one.

15 Number two, how many of the deaths and
16 very serious adverse events were associated with
17 GHB use alone?

18 DR. FALKOWSKI: I believe you could
19 address the reliability of DAWN. You are a DAWN
20 reporter. Again, regarding the deaths, you know,
21 the Drug Abuse Warning Network also collects data
22 from medical examiners, but the people in the
23 20-city work group of mine rely more often on
24 getting data directly from the medical examiners,
25 first because it is more timely and also because it

1 casts a better net. It captures situations that
2 are not only due to drug-related toxicity but also
3 ones where the use of drugs were considered by the
4 medical examiner to be significant contributing
5 factors to the death. So, that is what I can say
6 about deaths.

7 Also, I have a table, if you are
8 interested, that I could make available that shows
9 exactly DAWN emergency room data for 1999 and what
10 were the co-ingestants.

11 DR. KAWAS: Our next speaker is Dr. Jo
12 Ellen Dyer, from the California Poison Control
13 System at UCSF, speaking on adverse medical effects
14 with GHB.

15 Adverse Medical Effects with GHB

16 DR. DYER: Thank you and good afternoon.

17 [Slide]

18 In 1990 I identified and made the first
19 reports on GHB abuse from over-the-counter sales of
20 GHB. Over the next 11 years I have been following
21 GHB. I have an interest in it and I have been
22 reporting on the progress, the adverse effects and
23 the trends in use.

24 [Slide]

25 This is a description of the California

1 Poison Control System data of GHB reports to our
2 center. We logged these reports over 10 years.
3 The first years are when the San Francisco center
4 stood alone so it is a population base of 7 or 8
5 million. We became a system in '97 so we have 4
6 years of data for the entire state.

7 We are a medical toxicology consult
8 service, so we are not a required or mandatory
9 reporting center. So, this reflects just the tip
10 of the iceberg of use and abuse and adverse effects
11 that are out there.

12 [Slide]

13 In our experience GHB produces a profound
14 coma. This has been known for over 40 years,
15 starting out in surgical anesthetic studies where
16 it was evaluated as an anesthetic and now through
17 numerous occurrences of coma in users through this
18 widespread public use, where accidental overdoses
19 are occurring because of the narrow and variable
20 therapeutic index for this drug.

21 [Slide]

22 Looking at 5 studies, anesthetic studies
23 that cover over 700 patients -- there are many
24 other studies; I just picked a small set of them --
25 you see the effects of GHB in a controlled

1 situation. GHB causes unconsciousness and a
2 profound coma. This is what is intended with an
3 anesthetic. The respiratory effects that are seen
4 are Cheyne-stokes respiration. There were
5 aspirations. There was a case of unexplained
6 pulmonary edema. In many of these cases the
7 patients are intubated and the airway is attended
8 to. If their airway was left to chance in these
9 situations, it would be compromised. They lose
10 their airway protective reflexes. They have no
11 gag. So, with the high incidence of vomiting,
12 about 30 percent in these studies, combined with
13 the loss of gag, it is not difficult to see how
14 aspiration is going to occur.

15 There are cardiovascular effects, like
16 bradycardia, and then there are isolated incidences
17 where blood pressure rose up to 30-60 mmHg for
18 unexplained reasons really. There is myoclonus
19 that we see. There is an emergence delirium,
20 confusion. There are also secretions like
21 salivation, vomiting, incontinence and diaphoresis.

22 [Slide]

23 If I look at 16 reports that cover 175
24 cases of adverse events where GHB was in public
25 use, you see these same physiologic responses to

1 GHB. You have profound coma. They develop a mild
2 respiratory acidosis; bradycardia; myoclonus;
3 confusion; emergence delirium; and then the
4 secretions. This raises doubts for safety of use
5 among a generalized public population.

6 [Slide]

7 If we look at a closer group where we did
8 a study in our emergency department, and this is
9 the San Francisco County emergency room that sees
10 over 200 patients a day -- we looked at GHB
11 overdoses that we had over 3 years. This is just a
12 retrospective descriptive study where we were
13 trying to get a handle on what is going on. We
14 found that of those cases, about 33 percent had no
15 co-ingestion. This was documented by either
16 toxicology or patient report. Those patients came
17 in, a quarter of them, with Glasgow Coma Score of
18 3. So, they were profoundly comatose and 33
19 percent of them had coma scores between 4-8. The
20 coma lasted 15 minutes to 6 hours.

21 Again, a third of the patients had these
22 same symptoms, bradycardia, respiratory acidosis,
23 hypothermia, vomiting. We saw hypotension in about
24 11 percent. Those cases were primarily cases where
25 alcohol was co-ingested. Then, on emergence these

1 patients are difficult to manage. They can have an
2 emergence delirium which includes combative,
3 agitated behavior.

4 [Slide]

5 Because of that evidence and wanting to
6 focus in closer and get some GHB levels to find out
7 if that is truly what we were looking at, we did a
8 prospective study over 6 months, looking at 15
9 cases of GHB overdose, and 73 percent of those came
10 in with a Glasgow Coma Score of 3. Our intent was
11 to document the presence of GHB, to detect the
12 co-ingestants and what they were or if there were
13 none, and then to verify that our ability to
14 predict an overdose is truly GHB by the toxidrome
15 that we are using, whether or not that was
16 effective.

17 So, all of these 15 cases did have GHB
18 that was measurable. They were young, ages 20-39;
19 73 percent were male. The study inclusion criteria
20 were patients presenting with Glasgow Coma Scores
21 less than 8 and 73 percent of these patients had a
22 Glasgow Coma Score less than 3.

23 In 5 of the cases there were no other
24 drugs or alcohol detected. The GCS was 3 in 80
25 percent of those cases. So, profound coma from

1 accidental overdose; no other obvious cause.

2 [Slide]

3 It is clear to us that there is really
4 substantial evidence that GHB causes coma. Coma is
5 life-threatening, and these deaths are occurring
6 from accident or injury and from respiratory
7 compromise. We are seeing that through aspiration;
8 through apnea; through positional asphyxia -- these
9 are profoundly comatose people, they can't even
10 move to open their airway -- and through pulmonary
11 edema.

12 [Slide]

13 So, I have reviewed 20 GHB related
14 fatalities where I had autopsy reports. I just
15 sent letters to medical examiners asking for their
16 reports. In these cases, the ages ranged from 15
17 to 46 years. Three-quarters of them were male; 20
18 percent of them had no concurrent ingestions. If
19 we look at those that had co-ingestants, the 80
20 percent. We will see that many of these substances
21 are legal commonly ingested things. Tylenol was
22 one of them; caffeine; alcohol. The levels of
23 alcohol went up to 0.17 percent. The legal limit
24 for driving ranges from 0.08 to 0.1. So, most of
25 these cases were in the lower range, right around

1 the legal limit of driving, saying that they had
2 maybe one or two drinks and none of these would
3 reach an alcohol level that would cause coma.

4 [Slide]

5 The societal costs that were seen from GHB
6 abuse, there are many driving under the influence
7 arrests that have occurred with GHB. There were a
8 whole lot that were not recognized until GHB
9 testing became available and now they are being
10 recognized. I don't go out really and collect this
11 data but there are two vehicular manslaughter, I
12 guess they would call it, cases where a person
13 driving under the influence of GHB has hit and
14 killed another individual. One of those was in '96
15 and one was in 2000.

16 Another societal cost is the assaults
17 where the victim is under the influence of GHB
18 given to them or slipped to them by the assailant.
19 It is common enough that they have a term for it.
20 It is called being "scooped" by GHB. The assailant
21 then attacks the victim while they are unconscious
22 or amnestic to the effects of the drug, making
23 prosecution and even reporting of these very, very
24 difficult.

25 These are 4 cases. There are others. But

1 in these GHB was clearly documented as the cause.
2 The first was a woman who was drugged and assaulted
3 by her boss as they went out with a group of
4 colleagues after work. She had GHB in her urine.
5 There were 10 victims of some DJs in Los Angeles
6 that were slipping GHB into drinks and then
7 assaulting them. There was a 24-year old that was
8 eventually prosecuted more for trafficking drugs
9 after a woman had reported an assault to them and,
10 in kind of the bargaining, he admitted, yes, he had
11 drugged her twice with GHB and she has no memory of
12 the first event at all. Nothing. The last is two
13 15-year old females who were unconscious at a
14 party. One was hospitalized and one of these girls
15 died.

16 [Slide]

17 We also see addiction as another burden
18 from GHB abuse. We are currently seeing one to two
19 cases a month at our poison center, and this is
20 eight cases that I collected. The age range is
21 young, 22-38, again three-quarters male. The
22 pattern just continues through all these of the
23 demographics of who is using. Of these, 63 percent
24 started taking GHB for body building. They had
25 what they thought was kind of a legitimate use of

1 this dietary supplement. In this group, 88 percent
2 of them were employed or students. These were
3 functional members of society that have had trouble
4 now because of this drug. These are not people
5 that really had drug-seeking behavior. The onset
6 of symptoms we see within 1-6 hours. It progresses
7 over a couple of days. The duration is 5-15 days.

8 Now, these are often unrecognized by
9 healthcare professionals when they present for
10 treatment. GHB abuse addiction is not really very
11 well known out there. These are severe
12 neuropsychiatric symptoms with autonomic
13 instability that we see. I have had physicians who
14 have treated many, many cases of severe alcohol
15 withdrawal that have called me up and said, my
16 gosh, I am impressed; I am so impressed by this
17 withdrawal symptom. The patients become agitated,
18 combative, delirious. They are hallucinating.
19 They require sedation, a milligram a minute of IV
20 Ativan has been used over a few hours to gain
21 control. They require four-point leather
22 restraints and intensive care. One of the
23 patients in this series died while being
24 hospitalized for GHB withdrawal.

25 [Slide]

1 Substantial and compelling evidence from
2 case reports of accidental poisoning and from
3 toxicology supported adverse events really shows us
4 that these effects are due to GHB. It is not some
5 contaminant or something else that is causing
6 these. And, there is an insufficient or no safety
7 margin between the effective level of the
8 therapeutic dose of these drugs that these people
9 are taking and the dose that causes these effects.
10 As you can see from the sponsor's study, the
11 adverse effects that they are reporting are very
12 similar. The confusion, the nausea, the vomiting
13 are very similar to the things that we are seeing.

14 One physician, Dr. Gallamberti from Italy,
15 who is doing therapeutic use of GHB withdrawal
16 states talks about a 15 percent problematic GHB use
17 among his population. This can be dose escalation.
18 This can be GHB overdoses up to 10 times a year, or
19 GHB dependence.

20 [Slide]

21 This slide just looks at the kinetics to
22 illustrate that there is really a very narrow
23 therapeutic index with this drug and there is a lot
24 of variability. The pharmacokinetics of GHB are
25 capacity-limited absorption, capacity-limited

1 elimination. The coefficient of variation of some
2 of these parameters is 50 percent. There is a lot
3 of variation and we don't really know what the
4 consequence in different populations and different
5 people of these really variable kinetics is going
6 to be, or why they are so variable. You are used
7 to using phenytoin. It has capacity-limited
8 elimination. We know that when you are bumping the
9 dose of a patient on phenytoin you have to be
10 really careful because they can exponentially
11 increase their level. Well, the same thing happens
12 with GHB and we don't know where that is yet.
13 There is not enough experience. And, with
14 phenytoin the absorption is pretty good. We know
15 the bioavailability of IV phenytoin and oral
16 phenytoin. Here, I don't think it is so constant.
17 It really changes with food and there is a
18 capacity-limited absorption that is going to vary
19 between patients. So, this is a really difficult
20 drug to control, particularly orally on an
21 outpatient basis.

22 [Slide]

23 So, what is the current level of GHB abuse
24 that is out there? We really don't know. If we
25 wanted to project from one survey that was done,

1 Dr. Miotto, a UCLA physician that works addiction
2 medicine did a 45-minute structured interview with
3 42 GHB users. Among that group, 69 percent had
4 admitted that they had lost consciousness, had
5 periods of consciousness laps from minutes to
6 hours. There was variability in the amnesia
7 dependent upon how often people used. Twenty-eight
8 percent admitted having an overdose; 9 percent had
9 been to the emergency department for an overdose.

10 Now, there is an interesting misconception
11 here where they don't consider the loss of
12 consciousness to be an overdose, and people
13 overdose and when they are in a profound coma are
14 not taken to the emergency department. So, there
15 are really some problems there, and this gives us
16 an example of the kind of under-reporting that is
17 out there.

18 If we try and extrapolate from the amount
19 of drug that we are seeing marketed illicitly, this
20 is just one arrest in Marin County, a small county
21 north of San Francisco, where they had 207 L of
22 butanediol. The average street dose varies around
23 2 g. If you look at that, that is 103,500 doses in
24 one capture at one house, and there are many, many
25 of these. There are lists of different amounts

1 that have been busted all over.

2 Then there is the problem that Carol has
3 already talked about, surveying and policing the
4 issues of this type of new drug abuse. There is no
5 systematic method in place for data collection on
6 this.

7 There is rapid metabolism of the drug. It
8 clears from the blood in within about 6 hours; it
9 clears from the urine within about 12 hours. We
10 can't test these people and find it. When we are
11 trying to get evidence in a drug assault case, it
12 is gone. It is really difficult to detect. And,
13 should we increase our level of detection to the
14 very, very minute nanogram kind of range, then we
15 are going to start running into the biological
16 background so we aren't even going to be able to do
17 that if we increase our ability to detect. There
18 are also very poor assays currently out there.
19 None of the hospitals have an assay for this, and
20 none of the law enforcement has a field kit for it.
21 So, it has to be taken into a lab and specifically
22 run through a complicated GC mass spec procedure to
23 get a level out, which is expensive.

24 The current documentation clearly grossly
25 underestimates the amount of use that is out there.

1 And, it is very clear that there is a little, if
2 any, safety margin with GHB use in the therapeutic
3 doses that are proposed. GHB is a very potent new
4 drug of abuse. It has been around 10 years. We
5 thought it was going to come and go as a fad, it
6 hasn't and it is not going to. The use is still
7 increasing.

8 There is a very high acute toxicity in
9 accidental overdose -- coma, bradycardia,
10 myoclonus, vomiting, aspiration -- we are seeing a
11 lot of it, and it has very high abuse and addiction
12 potential. So, I think that we have to be very
13 careful and it is very difficult to try and
14 minimize these potential risks, the risks of having
15 it get out into the drug abusing population but
16 also among patients that we are going to be giving
17 this drug to take at home. At the poison center,
18 every night at bedtime, 9 to 11 o'clock I am called
19 by people that say, oh, I'm sorry, I accidentally
20 took a double dose of my medication. What should I
21 do? In this case, they are all going to go to the
22 emergency room. There is really not a margin of
23 safety with this drug. Thanks.

24 DR. KAWAS: Thank you, Dr. Dyer. The next
25 presentation is from the sponsor, presentation on

1 risk management and abuse liability, Dr. Bob
2 Balster, from the Medical College of Virginia.

3 DR. REARDAN: Yes, I would like to now
4 introduce Dr. Balster who will present his views
5 with respect to abuse liability of Xyrem and GHB.
6 Dr. Balster is a previous chair of the FDA Drug
7 Abuse Advisory Committee and a widely published
8 abuse pharmacologist from the Medical College of
9 Virginia. He is editor and chief of a leading
10 addiction journal, Drug and Alcohol Dependence, and
11 a past president of the College on Problems of Drug
12 Abuse.

13 Sponsor Presentation on Risk Management
14 and Abuse Liability

15 DR. BALSTER: Thank you very much, Dayton.
16 Good morning or good afternoon, I guess it is now.

17 [Slide]

18 Well, as you have just heard, the
19 development of Xyrem as a medication has taken
20 place in a context of a national epidemic of the
21 abuse of its constituent GHB, and also the abuse of
22 a number of GHB-related drugs that I will tell you
23 about.

24 As Dr. Houghton told you, Orphan is very
25 well aware of this problem and has consulted many

1 drug abuse experts to try to understand the problem
2 better. My own analysis of this situation is that
3 Xyrem has certainly not contributed to the problem
4 that exists today with the abuse of this class of
5 compounds. I guess where I may disagree a bit is
6 that I am pretty convinced that Xyrem is not going
7 to be a player in this over the long term.

8 I think in order to understand and make an
9 appropriate public health response to this
10 situation, you need to know a little bit about what
11 some of the causes are of this GHB abuse problem.

12 [Slide]

13 So, I hope to make two points in this
14 presentation. The first point is that I believe
15 that the recent abuse of GHB-like substances
16 probably reflects a ready availability more than
17 their inherent pharmacological propensity for
18 abuse.

19 I think I will make this point by first
20 off reviewing for you the incredible availability
21 of these compounds, and then also review very
22 quickly scientific studies that have been done on
23 the abuse liability of GHB as it is compared to
24 other drugs of abuse you might be familiar with.
25 Secondly, I believe that Xyrem, if approved for

1 medical use, will not contribute to the public
2 health problem of the abuse of these GHB-like
3 substances in any significant way.

4 [Slide]

5 Before we continue, it is very important
6 to know the cast of characters here. I think next
7 to the federal government, the next worst developer
8 of abbreviations is a drug abuse research
9 community, with MDMA, and PCP, and GHB, and BD --
10 it must be hard to kind of keep track of the
11 players but, of course, the drug we are talking
12 about here is GHB, gamma hydroxybutyrate. But
13 there are a bunch of other drugs that are basically
14 part of this national drug abuse problem.

15 You have heard a little bit about them,
16 but these precursors, gamma butyrolactone or GBL,
17 1,4 butanediol or 1,4-BD are precursor compounds
18 that, if obtained, can be easily and readily
19 converted into GHB. They also can be consumed
20 directly because they are metabolized by the body
21 into GHB. So, they themselves are drugs of abuse
22 like GHB. Then there are others that are also
23 available.

24 Now, of all these chemicals only GHB is
25 actually a scheduled drug. It is Schedule I under

1 the Controlled Substances Act for the abusable
2 versions, GHB; Schedule III for an approved medical
3 product. So, only GHB is scheduled. Now, GBL is
4 what is called listed so its availability is
5 diminished. These others are still freely
6 available without any drug abuse controls.

7 [Slide]

8 You have heard a lot about GHB abuse but I
9 am pretty convinced that what we are seeing here is
10 something that has resulted from an amazing
11 situation of the availability of these compounds.
12 To remind you, GHB was available legally and
13 legitimately through health food stores up through
14 1990 when you could buy it anywhere, and the abuse
15 problem with this drug began during that period of
16 time.

17 Then through that time and afterwards GHB
18 could be obtained through the Internet. There was
19 an amazing number of sites set up to sell GHB.
20 Then, as GHB became less easy to get because
21 Internet sources dried up, the Internet sources
22 were selling the precursors, etc., etc. I will
23 show you some data a little bit more, but these
24 precursors are not going to disappear any time soon
25 from public availability. Now that the

1 availability of GHB has been restricted by the
2 federal scheduling actions and actions by the FDA,
3 people can now purchase the precursors and make
4 their own GHB. Essentially anyone can do that. It
5 is a very simple thing and the recipes are right
6 there on the web. As I said before, they
7 themselves are widely abused. So, we have a class
8 of chemicals here that are really basically part of
9 what has been referred to as a GHB abuse problem,
10 but it is really an abuse of a class of drugs, and
11 you saw some evidence on that.

12 [Slide]

13 At this point I want to review the
14 scientific literature on the laboratory studies of
15 the abuse potential of GHB. You may wonder why I
16 would want to do that, I mean, why would I want to
17 review literature on abuse potential when the
18 reality of GHB abuse is clear to us from
19 epidemiological data that Dr. Falkowski mentioned
20 and clinical data. The reason to do this is to try
21 to understand what the basis for this is, and to
22 know whether or not this wide abuse is due to some
23 features of this incredible availability, or
24 whether the drug has sort of the inherent
25 pharmacological desirability that you would

1 associate with a really dangerous drug like cocaine
2 or heroin where, no matter how many billions of
3 dollar we throw at the problem, we are getting
4 nowhere with it, or does GHB represent a drug which
5 is less desirable or has less propensity for use.

6 [Slide]

7 Just to remind you, there is a
8 well-established science of abuse liability
9 evaluation, and it is used in evaluating new
10 compounds that are under development. It is useful
11 in making decisions about drug abuse control, and
12 data such as these are used widely by the FDA for
13 making regulatory decisions. All of these data are
14 reviewed in your packages, but just to quickly tell
15 you, first off, GHB is a unique drug. It is not
16 just another depressant drug like barbiturates or
17 even benzodiazepines that have its own receptor and
18 its own characteristics.

19 In studies which are called drug
20 discrimination studies, which allow you in a way to
21 compare unknown drugs to known drugs of abuse,
22 again, GHB lacks equivalence to these classical
23 depressants like barbiturates or any other classes
24 of drugs to which it has been directly compared.

25 In self-administration studies -- these

1 are laboratory studies where you can actually
2 measure what we call the reinforcing effects of the
3 euphorigenic potential of these drugs -- actually
4 in this particular class of studies GHB has very
5 weak reinforcing effects. It is difficult to
6 obtain them in laboratory studies and there have
7 been a number of those. We did one of these
8 ourselves in our laboratory and we essentially
9 found no evidence of GHB self-administration under
10 conditions where we reliably get
11 self-administration of cocaine, heroin,
12 barbiturates, etc., etc.

13 The case of physical dependence is a
14 little bit more complicated. You heard from Dr.
15 Dyer about the fact that abusers can develop
16 dependence and show withdrawal signs, and there is
17 no question about that. These people are taking
18 maybe 10 or more times the therapeutic dose. We
19 are talking about 70, 80, 100 grams a day, and they
20 take them every 3 hours or so because they have to
21 maintain the blood level. Yes, in those cases you
22 get dependence, but in patients receiving Xyrem,
23 where they are getting it in lower doses and they
24 are taking it only in the evening, as you have
25 heard from the reports, there have not been

1 significant problems of dependence. So, yes, it
2 can occur in abusers but it isn't really an issue
3 in patients. Importantly, animal studies, for
4 example, where you try to show the dependence of
5 GHB and compare it, for example, to barbiturates,
6 it is not easy to develop a model for GHB
7 dependence in animal studies because it has less
8 inherent dependence producing properties than these
9 other drugs.

10 [Slide]

11 So, my conclusion when I reviewed the
12 literature on the scientific studies of GHB, when I
13 was asked to do that, I basically thought it looked
14 a lot like what I would say is a Schedule IV drug.
15 Schedule IV drugs, you remember, are
16 benzodiazepines and chloral hydrate and drugs of
17 this type, and that is sort where it fit. It isn't
18 like cocaine. It isn't like heroin. In fact, that
19 analysis of looking at the data has been made by
20 others with very much the same recommendation as
21 mine, that is, it sort of fits pharmacologically
22 with Schedule IV.

23 For example, the WHO expert committee
24 which met not too long ago to make a recommendation
25 to the UN Commission, the WHO expert committee

1 recommended Schedule IV and, in fact, the UN
2 Commission ultimately placed GHB in Schedule IV.
3 Schedule IV, under the Psychotropic Convention is
4 very analogous really to our Schedule IV that you
5 are familiar with under the Controlled Substances
6 Act.

7 [Slide]

8 We are not here to talk about GHB abuse
9 which we know is a significant problem. We are
10 here to talk about Xyrem and what its role may be
11 in the drug abuse problem in the United States.
12 There are two issues we are really worried about
13 here. Number one, we are worried about the
14 possibility that patients legitimately prescribed
15 Xyrem will abuse it in some way, or misuse it or
16 escalate and then, secondly, we are worried about
17 whether or not it might be diverted into sort of
18 illicit channels and become part of a problem in
19 that way.

20 [Slide]

21 Turning first to the issue of patients,
22 first off, I think most of you know, and it is
23 important to always know this, that the development
24 of abuse among patients receiving therapeutic doses
25 of abuse drugs is a much smaller problem than some

1 people realize. It is actually fairly unlikely to
2 occur in a general sense. Of course, in the trials
3 with Xyrem there weren't problems of abuse; there
4 wasn't evidence that people were escalating their
5 dose or complaining and asking for more, and that
6 sort of thing.

7 It is important also to recognize that
8 narcolepsy patients are patients that are receiving
9 controlled substances all the time. The stimulant
10 class of drugs, all those drugs that Dr. Mignot
11 spoke about are all scheduled compounds. In fact,
12 many of them are Schedule II where they can't even
13 get them half the time because the production
14 controls on Schedule II reduce their availability.

15 Then the issue about their dependence, if
16 you understand, for example, that with
17 benzodiazepines, when you discontinue
18 benzodiazepine administration you will often see a
19 withdrawal syndrome, well, that is because
20 benzodiazepines have this incredibly long duration
21 of action with active metabolites that accumulate
22 so that the body continually maintains levels of
23 benzodiazepines. So, when you quit using them
24 there is a withdrawal syndrome. With GHB, as you
25 saw from Dr. Houghton's presentation, the duration

1 of action is just a couple of hours. It would take
2 many, many, many multiple daily uses, way more than
3 the patients are going to get, to maintain the kind
4 of levels of GHB that would be expected to produce
5 dependence. So, yes, in abuse cases where people
6 are just going all day and all night but not with
7 patients.

8 [Slide]

9 Turning now to illicit diversion of Xyrem,
10 first off, that hasn't happened yet. So, we are
11 not aware of any diversion of any Xyrem through any
12 of the products. This is, of course, only in
13 clinical development but I think it is important to
14 know. Most importantly, the company has been very
15 much worried about this issue and has developed a
16 distribution system that you are going to hear
17 about, called the Success Program, which I
18 personally believe is going to substantially
19 prevent any opportunities for diversion. Lastly,
20 Xyrem, whether you approve it or not -- it is going
21 to make very little difference in the overall
22 availability of this whole class of chemicals in
23 the national scene.

24 [Slide]

25 To illustrate that, this slide shows you

1 the product amounts anticipated, annual production
2 amounts for this class of chemicals I mentioned to
3 you. So, if Xyrem is approved the anticipated
4 first year production amounts of gamma
5 hydroxybutyrate are about 82,000 kg. GBL, gamma
6 butyrolactone, the precursor that can be made into
7 GHB easily and consumed itself, is 83 million kg, a
8 thousand times more. 1,4-BD which is not a
9 controlled substance and has no drug abuse control
10 under it whatsoever right now, is widely available
11 through all sources in large amounts, and is made
12 in the neighborhood of 377 million kg. For those
13 of you who don't do the metric system, that is
14 400,000 tons of 1,4-BD. And, all of these drugs
15 are basically substituting for one another. So,
16 whether you take Xyrem in or out of that graph, it
17 is not going to make a difference.

18 [Slide]

19 In conclusion, I believe that the epidemic
20 of abuse of GHB-like drugs has resulted really
21 primarily from its extraordinary availability. In
22 fact, when GHB was controlled -- it is hard now to
23 get GHB. It is hard even for me to get GHB as a
24 research scientist. So, the problem has now
25 switched to these precursors that are available.

1 Secondly, the scientific studies of GHB
2 show that you are not talking here about cocaine or
3 heroin. It is a weak depressant of maybe the
4 benzodiazepine, chloral hydrate type. Thirdly, I
5 believe that Xyrem abuse is very unlikely among
6 patients for the reasons I said. Lastly, the
7 contribution of Xyrem to the public health problem,
8 which is the matter of concern, is essentially not
9 significant. So, you know, have your way with the
10 drug in terms of efficacy and safety but I don't
11 think you need to be worried that this drug is
12 going to be a major factor in the drug abuse
13 problem with this class of drugs. Thank you.

14 DR. KAWAS: Yes, a quick question, Dr.
15 Leiderman.

16 DR. LEIDERMAN: Yes, I would like to ask
17 Dr. Balster two questions. I would like you to
18 comment on the species of animal that you are
19 addressing when you talk about self-administration
20 in drug discrimination studies. Two, I would like
21 you to comment on the data that those models show
22 with other classes of drugs.

23 DR. BALSTER: All the studies are reviewed
24 on that slide on abuse potential with laboratory
25 animal studies, using fairly well developed

1 methodologies. The self-administration studies
2 that Dr. Leiderman referred to were studies that
3 were done in monkeys in sort of a standardized
4 method that is done through a program directed by
5 the College on Drug Dependence. Those are the
6 models, and I can show you data if you give me the
7 time to do it. Maybe later, if the committee is
8 interested, I can show you data. But these are
9 models in which basically it is extremely easy to
10 get animals to actually literally self-inject most
11 of the drugs of abuse -- cocaine, amphetamines,
12 opiates of all types, barbiturates, depressants,
13 benzodiazepines -- benzodiazepines are a little
14 harder but in the model that was used that I showed
15 the negative results from, benzodiazepines were the
16 positive control. So, basically the only area
17 where that model has been not very successful and
18 underestimates abuse potential is with
19 hallucinogenic drugs and marijuana type drugs.

20 DR. LEIDERMAN: Yes, many of the Schedule
21 I drugs. DR. REARDAN: We just
22 have about another ten minutes. If we can prevail
23 on the committee, we have one last speaker, and
24 that will be Patti Engel, who is going to describe
25 for you the risk management system that the company

1 has developed to help control diversion. Patti?

2 Risk Management

3 MS. ENGEL: Good afternoon. My name is
4 Patti Engel, and I am here today to talk to you
5 about the risk management program for Xyrem, which
6 we call the Xyrem Success Program.

7 [Slide]

8 This program will ensure the responsible
9 distribution of Xyrem, namely, to meet two goals.
10 First, to ensure that patients who desperately need
11 the medicine can get it. Secondly, to keep this
12 out of the hands of those people who might abuse
13 it.

14 [Slide]

15 To develop this program we consulted
16 broadly with a number of people interested in the
17 issues not only germane to patients but also that
18 of drug abuse. As you can see, we spoke with drug
19 diversion investigators, field law enforcement,
20 forensics experts, toxicologists, pharmaceutical
21 distribution experts, drug abuse trend experts.

22 [Slide]

23 Through those discussions we followed
24 FDA's proposed risk management guideline, which is
25 risk management through risk confrontation, in

1 essence egging the partners and the shareholders to
2 not only identify the issues but also assess the
3 risks, identify the options and select a strategy.
4 The program that I am going to be sharing with you
5 today is certainly a draft program that the company
6 has designed after discussions with these numerous
7 stakeholders.

8 [Slide]

9 This slide I show to you really to point
10 out the standard route of distribution of a
11 pharmaceutical product in our country today. This
12 includes not only commonly used medications like
13 products for blood pressure control or products for
14 arthritis, but also products under Schedule II,
15 including such agents as amphetamines. Typically,
16 a product is manufactured and goes to a number of
17 national, regional and local wholesalers,
18 eventually getting to 63,000 retail drugstores
19 around the country. One can only imagine the
20 number of loading docks, transport vehicles and
21 hands that touch a pharmaceutical product in this
22 traditional distribution system.

23 [Slide]

24 As we contemplated the distribution of
25 Xyrem and how to do this responsibly to meet the

1 prior stated goals, we determined that a closed
2 distribution system would best fit everyone's needs
3 for this product. The product is manufactured at
4 one single manufacturing facility. It is sent to
5 one single national specialty pharmacy. Eventually
6 it goes by courier to patients with narcolepsy.

7 [Slide]

8 The benefits of this program are that not
9 only is the product distributed from a central
10 location, but all the controls and all the records
11 are in one place.

12 [Slide]

13 So, how will this work? Because a number
14 of doctors prescribe medicines for narcolepsy, we
15 will focus our promotional efforts on those
16 physicians. They include such specialists as
17 neurologists, pulmonologists, psychiatrists,
18 internal medicine physicians and several primary
19 specialties who practice sleep medicine.

20 [Slide]

21 Our small sales force will call on these
22 physicians, communicating the clinical benefits of
23 Xyrem in narcolepsy. At those calls, the sales
24 representatives will also review with each
25 physician something that we call the physician

1 Success Program. I will go into the details of
2 this program in a more in depth fashion in just a
3 moment. But it is important to know that each
4 physician will sign that they have reviewed this
5 program with the sales representative and
6 understand the program. I should also note that at
7 no time will we embark upon physician sampling.

8 [Slide]

9 I promised to come back to the components
10 of the physician Success Program. I know that many
11 of you received copies of this but I would like to
12 highlight some of the main points. First, because
13 we know individuals all learn differently -- some
14 by hearing, some by reading, other methods -- we
15 have made this a multi-faceted program which
16 includes videos, brochures, pamphlets that describe
17 four main areas.

18 The first is to highlight to physicians
19 that the distribution process for Xyrem is
20 different, that their patients won't be able to get
21 this at the corner drugstore. The second important
22 issue that this binder points out to physicians is
23 the dosing and administration of Xyrem. The next
24 important issue is that of home storage and secure
25 handling. The fourth is an important module that

1 we call "doctor be wary" which is an educational
2 module that educates doctors about the ways that
3 drugs are commonly diverted in this country so they
4 can be aware of patients who are attempting to
5 illegitimately get a prescription from them for
6 this product. Each of the kits will also contain a
7 number of unique prescribing forms for Xyrem which
8 will be necessary in order for the prescription to
9 be filled. This is, in essence, a special
10 prescription form. As well, contact information
11 will be provided should the doctor have any
12 questions at all about the program.

13 [Slide]

14 Once the physician decides to prescribe
15 Xyrem the physician faxes this special prescription
16 to the specialty pharmacy. Now, I am going to come
17 back to how this prescription is verified. So, I
18 will ask you to hold on that point for just one
19 moment. But, based on that prescription and based
20 on the patient's geographic location, the pharmacy
21 assigns that patient to a dedicated pharmacy team.
22 So, each time that the patient deals with the
23 system they are talking with the same pharmacist
24 and the same reimbursement specialist.

25 [Slide]

1 I mentioned that as the prescription comes
2 to the specialty pharmacy there will be a number of
3 checks to determine if the physician is, in fact,
4 eligible to prescribe Xyrem. We will be utilizing
5 DEA's NTIS or National Technical Information
6 Services database to ensure that each physician has
7 an active valid medical license, and also to ensure
8 that that physician has current prescribing
9 privileges which allow him or her to prescribe
10 Schedule III medications in this country. As a
11 backup check, the specialty pharmacy will also be
12 checking with the appropriate state medical board
13 to determine that there are no pending actions on
14 the behalf of the state for that given physician.

15 [Slide]

16 As a secondary step, the specialty
17 pharmacy will also do a check on the patient in
18 essence. What they will do is when that
19 prescription comes in they will call the
20 prescribing physician's office to determine that,
21 in fact, that patient is real and a prescription
22 has, in fact, been written for that patient.

23 [Slide]

24 Once insurance reimbursement is obtained,
25 the specialty pharmacy contacts the patient, first,

1 to determine the patient or the patient designee's
2 location and availability for shipment, and also to
3 describe to them the contents of the shipment. I
4 will come back to the details of this in just a
5 moment, but it is important that you know that each
6 patient, when they get their first prescription of
7 Xyrem will receive a multi-faceted educational
8 program called the Xyrem patient Success Program,
9 and I will come back to the details of that in just
10 a moment.

11 In that same shipment they will also
12 receive their Xyrem, and that will look something
13 like this, with child resistant closure not only on
14 the primary container but also on the dosing cups
15 which are provided by the company.

16 [Slide]

17 The shipment that goes to the patient is
18 sent by a special system that has a special, unique
19 tracking system called the Rapid Trac System. this
20 system will allow detailed real-time tracking of
21 that package which is delivered only by the
22 authorized signature. If the patient or their
23 designee is not available for receipt of the
24 package at the time agreed upon with the specialty
25 pharmacy, the package will be returned to the

1 specialty pharmacy after one delivery reattempt.
2 So, a package will not sit on a delivery truck or
3 in a hub for weeks at a time or anything like that.
4 If the package is lost the system will allow an
5 investigation to begin regarding the shipment's
6 whereabouts at that point of loss.

7 [Slide]

8 I spoke a moment ago about the patient
9 Success Program. Again, this is a multi-faceted
10 program which includes video, brochures and
11 pamphlets which deal with a number of important
12 issues for patients. First addressed, of course,
13 is the distribution process since it is so
14 important that the patients understand that the
15 only way they will get Xyrem is through the special
16 pharmacy and not at their corner drugstore.

17 There is information about Xyrem's dosing
18 and administration because we feel that that is an
19 important message to be delivered in an
20 understandable and a very consistent manner.

21 There is information on home storage and
22 secure handling, and we also are very clear with
23 patients about the criminal and civil penalties
24 that the public law assigns to any illicit use of
25 Xyrem. So, if I were, as a valid narcolepsy

1 patient, to take my Xyrem prescription and use it
2 to conduct a rape or in an assault situation, or if
3 I were to sell it to someone for illicit use I
4 would be penalized, I would be subject to C-I
5 penalties. The patient Success Program also
6 includes contact information for the specialty
7 pharmacy should the patient have any questions at
8 all, and also reimbursement information.

9 [Slide]

10 After the Rapid Trac System shows that the
11 package has been received by the patient, the
12 specialty pharmacist will call the patient within
13 24 hours not only to confirm receipt of that
14 package but also to again reiterate certain
15 important points with the patient. Those include
16 the penalties for illicit use of Xyrem; Xyrem's
17 dosing and administration; home storage and secure
18 handling. The pharmacist will also take the
19 opportunity to discuss with the patient the
20 child-resistant features on the primary container
21 as well as the child-resistant features on the
22 dosing cups that are provided.

23 [Slide]

24 The central data repository designed for
25 Xyrem really allows for identification of a number

1 of unusual types of behavior, including any
2 duplicate prescriptions, any attempts of
3 over-prescribing, or any attempts at over-use by
4 patients. The benefit here is that that
5 information is available prior to filling the
6 prescription so appropriate pharmacist intervention
7 can occur.

8 [Slide]

9 As you can see, the Xyrem Success Program
10 is a comprehensive program which is designed to
11 responsibly distribute this important medication in
12 order that patients who need it have it available,
13 and it is inaccessible for those who might abuse
14 it. Thank you.

15 DR. REARDAN: Dr. Kawas, that completes
16 our presentation and we will turn this back over to
17 you.

18 DR. KAWAS: Thank you very much. I want
19 to thank all of you for all of your nice
20 presentations but, rest assured, you will have more
21 questions in the afternoon. We are running quite
22 late so we are going to cut lunch a little short
23 and we will plan on reconvening at 1:30, at which
24 time the public hearing component of this meeting
25 will happen.

1 [Whereupon, at 12:50 p.m., the proceedings
2 were recessed for lunch, to resume at 1:30 p.m.]

1 A F T E R N O O N P R O C E E D I N G S

2 DR. KAWAS: We will reconvene the meeting
3 of the Peripheral and Central Nervous System
4 Advisory Committee discussing Xyrem. We are now in
5 the open public hearing portion of this meeting,
6 and we have quite a few people that we will be
7 hearing from and additional people who want to add
8 to the list. I would like to ask all of the
9 speakers to please do their best -- not their best,
10 you must stay to five minutes. You will have a
11 one-minute warning sign with your timer. If you go
12 over, please don't take it personally but you might
13 hear my voice ending your part for the meeting.
14 This is in order to allow us to hear from everybody
15 who wants to speak, as well as to get onto the
16 deliberations of this committee. The first speaker
17 in the public forum is Sharon Fitzgerald of
18 Littleton, Colorado.

19 Open Public Hearing

20 MS. FITZGERALD: Good afternoon. I am
21 Sharon Fitzgerald from Littleton, Colorado, and I
22 am a narcoleptic. I am a volunteer member for the
23 Orphan Medical Patient Council and the Narcolepsy
24 Network is paying for my travel and my hotel to
25 allow me the privilege of speaking with you today.

1 Five minutes isn't long enough. I have provided a
2 longer version for you to read. Please, please
3 read it. It explains my experiences with the five
4 major symptoms of narcolepsy and how Xyrem gave
5 back my American dream, the ability to pursue
6 happiness without stumbling on the way when it gets
7 tough, and without literally falling on my face
8 when the goal of happiness is reached.

9 I have had daytime sleepiness since 1969.
10 It threatened my ability to be a good mother and
11 protect my children, and it trapped me in a series
12 of entry level jobs. Not knowing it had a name, I
13 tried to hide my problem from employers and I hid
14 in restrooms for many years for 15-minute naps at
15 unpredictable times lots of the time.

16 My symptoms dramatically increased and
17 worsened in 1977 when I was in law school. I was
18 raising school age kids on my own, being widowed at
19 the age of 32. In daytime, against my will, I took
20 naps in my classes, going instantly from
21 consciousness to dream state sleep, the switch
22 being so quick that I actually wrote words from my
23 dreams in my class notes about things like my
24 mother and helicopters, and wondered where they
25 came from when I read them. These were usually

1 followed by a mark where I dropped my pen as I
2 stopped writing, and that would startle me into
3 wakefulness and I would stay awake for a while and
4 take more notes.

5 Going to sleep nearly every night, my mind
6 created vivid illusions of my very worst fears,
7 often a murderous rapist breaking into my house
8 from behind wherever I was sitting or lying. My
9 knowledge of where I was, was accurate. I could
10 not scream. I was paralyzed and I couldn't turn
11 around to defend myself. These are called, as you
12 know, hypnagogic hallucinations. I didn't know
13 that at the time.

14 At the same time, the symptoms of
15 nighttime wakefulness became more severe. I
16 experienced long hours of anxiously lying awake,
17 punctuated by times of intense dreaming so real and
18 so vivid that in the daytime I couldn't remember
19 whether events I remembered were real or dreamed.
20 You may understand that I feared for my sanity, and
21 this is when I sought medical help.

22 I was my doctor's first experience with
23 narcolepsy. It took a very long time for him to
24 find a diagnosis. When he did, it was because of
25 my mild cataplexy and he found the diagnosis an

1 announced that was the good news because the bad
2 news was there was no treatment. I self-medicated
3 for years with Sudafed and coffee.

4 With determination -- if you knew me you
5 would know about it -- and special accommodations
6 from the university I actually finally managed to
7 graduate from law school, but I turned down the
8 dream job that was offered, clerking for a district
9 court judge, because I feared I would fall asleep
10 in front of the courtroom. He told me our first
11 case would be about two nuns who had been brutally
12 murdered and I feared I might experience cataplexy.

13 By this time my cataplexy had increased to
14 the point that all my facial muscles would relax
15 and my speech would become momentarily slurred. It
16 passed so quickly that I couldn't hide it. I was a
17 sole practitioner. I couldn't bill enough hours to
18 earn a living. I took Ritalin; I took
19 antidepressants unsuccessfully. I found a job with
20 the State of Colorado. It didn't require my legal
21 expertise but I got lucky, I found out about the
22 trials. I had rebound cataplexy, like what they
23 showed you in the pictures, and it was horrendous
24 for several weeks, waiting to be on Xyrem and my
25 secret was brought out at work. But they didn't

1 fire me because I told them I was going on Xyrem.
2 Its effects were immediate and dramatic.
3 I have experienced no side effects. I get good
4 restful sleep. I awaken refreshed. I stay
5 reliably awake at work with fewer stimulants and I
6 don't fall down. My supervisors noticed my
7 increased wakefulness and rewarded it with
8 committee chairmanships and memberships and, in
9 1999, a promotion. In 2000, January 1, I became an
10 administrative law judge for the Division of
11 Workers Compensation in the Colorado Department of
12 Labor and Employment. It is responsible; it is
13 emotional. I can do it. My colleagues know I have
14 narcolepsy and they know that with Xyrem it doesn't
15 interfere with my job performance. For years I was
16 unable to safely carry my children or
17 grandchildren. I carried my newborn to his first
18 examination and that is just the beginning of my
19 story.

20 DR. KAWAS: Thank you, Ms. Fitzgerald.
21 Next is Richard Gelula, the executive director of
22 the National Sleep Foundation.

23 MR. GELULA: Thank you. The National
24 Sleep Foundation is an eleven-year old organization
25 that was developed by the American Academy of Sleep

1 Medicine to educate the public about sleep and
2 sleep disorders, and our leadership has always been
3 drawn from the top tier of sleep experts, sleep
4 scientists and sleep physicians. We are
5 independent. We raise our money in a variety of
6 ways including government grants, corporate grants,
7 and many memberships, individual contributions that
8 have played a major part, particularly from people
9 and families affected by sleep disorders. Our
10 funding from Orphan Medical for the last two years
11 has been a total of 160,000 out of a two-year total
12 of about 5 million. Our budget is about 2.5
13 million a year. And, their support has gone to
14 broad activities -- sponsorship for National Sleep
15 Awareness Week where they join in with other
16 sponsors, and there is no name or brand specific
17 recognition or benefit for them. So, I wanted to
18 point that out.

19 The Foundation is qualified to address
20 this and our interest is due to the fact that we
21 have invested about a million dollars in narcolepsy
22 research, including center grants for the genetic
23 research done at Stanford. We presently have one
24 of our postgraduate fellowships at UCLA studying
25 the neurophysiology of cataplexy. We also have

1 established the National Narcolepsy Registry which
2 has registered to serum DNA registry with about 700
3 patients and family members registered. That is
4 managed at Montefiore Hospital in the Bronx, and it
5 has been a resource for seven scientific
6 investigations.

7 To summarize the position of the National
8 Sleep Foundation on sodium oxybate, the National
9 Sleep Foundation calls upon this panel to fully
10 consider the safety and efficacy of sodium oxybate
11 for the treatment of narcolepsy and cataplexy, and
12 to do so in a comprehensive context that fully
13 recognizes the extreme psychological, emotional,
14 economic, social and health toll that this
15 affliction exacts from people who suffer from it.

16 NSF does not presume to second-guess the
17 evidence that has been submitted about the safety
18 and efficacy of this drug, but it goes on record to
19 say that such considerations should only pertain to
20 affected patients and not other societal
21 considerations. It is safe and effective for
22 people with narcolepsy, like the speaker before me.
23 Sodium oxybate should be made readily available to
24 them. Any concern for illicit use should be
25 addressed strongly through other channels, such as

1 law enforcement and professional licensing. The
2 fact that narcolepsy is an orphan disease, for
3 which only one medication is currently indicated,
4 would be weighed as a factor in favor of approval
5 of sodium oxybate because it is likely that
6 availability of an approved drug will foster faster
7 diagnosis and more appropriate treatment, and will
8 also -- and we think this is very important --
9 stabilize patients who usually first experience the
10 dreadful effects of narcolepsy and cataplexy during
11 their developmental years, before the completion of
12 their educations and initiations of a career.

13 I would like to summarize a few key
14 background points. Narcolepsy and all of its
15 primary characteristics, including cataplexy, are
16 truly life-altering afflictions, a term that best
17 connotes the life-diminishing and debilitating
18 aspects of this disabling disease. Untreated,
19 narcolepsy not only causes vivid nightmares and
20 undermines the safe and secure feeling that most
21 people get when they go to sleep, but it makes
22 daily existence, both objectively and subjectively,
23 frightening and strange, even alienating to the
24 self and others. It makes the well-controlled
25 process that routinely governs the existence for

1 almost all other humans, the alternating cycle of
2 sleep and alertness, into something entirely
3 different, an uncontrollable process where the
4 maintenance of conscious attention becomes random
5 and cannot be sustained or relied upon. Both the
6 phenomenon of overwhelming sleep attacks and the
7 muscular weakness and collapse that occur with
8 cataplectic attacks undermine the sense of
9 predictability and confidence required to fully
10 develop and function in our contemporary world.

11 But a true understanding of narcolepsy
12 goes beyond physiology. The cumulative effects of
13 the distinctive daytime and nighttime
14 characteristics of this disease are truly
15 traumatic. They not only disrupt; they undermine
16 and frighten and change the core experience of the
17 individual, exacting a toll that ranges from
18 difficulty coping and functioning to total
19 disability.

20 I think some key characteristics that
21 should be taken into consideration are that
22 narcolepsy is not well understood or accepted.
23 People who suffer from this suffer alone. They
24 don't have generally the benefit of support groups,
25 even though there is a fine support organization

1 out there, but the people are just spread out.
2 There isn't enough concentration. Most people with
3 narcolepsy do not have a relative with the disease
4 such that it is even strange to them. People
5 suffer a double blow because it is thought their
6 sleepiness is volitional and a sign of laziness.

7 Thus, I think it should come as no
8 surprise that people with narcolepsy suffer from a
9 high rate of depression. It has been estimated
10 from 30-70 percent in various studies. The good
11 news is that in one study health quality of life
12 was improved through effective administration and
13 medical treatment, and I think that would pertain
14 as well to sodium oxybate.

15 In sum, the National Sleep Foundation
16 believes that narcolepsy exacts an unusual and
17 cruel toll. We really call upon this panel to
18 continue to do the professional job that brought
19 you here today and fully consider the personal,
20 psychological, emotional and human aspects of this
21 disease and the great need for an effective
22 medication. Thank you.

23 DR. KAWAS: Thank you, Mr. Gelula. The
24 next speaker is Ms. Abbey Meyers, who is president
25 of the National Organization for Rare Disorders,

1 Inc.

2 MS. MEYERS: The National Organization for
3 Rare Disorders, which is known as NORD, came
4 together initially because voluntary agencies for
5 many rare diseases worked together to pass the
6 Orphan Drug Act. So, we are the orphan drug folks
7 who work to monitor the development of these drugs.

8 I have several conflicts of interest with
9 this drug because for 20 years I begged practically
10 every company I ever met to pick up this drug and
11 to adopt it. It is a 20-year saga. And, I wrote
12 something for you that you will be able to read
13 about the history of development of the drug.

14 Also, about a year ago I bought some stock
15 in this company. If I wanted to make money I would
16 have put it in Merck, but the idea with the drugs
17 that they are developing is I feel I have to make
18 my own personal investment in the survival of the
19 company.

20 For this drug FDA, rightfully, has asked
21 for a risk management program, and there are
22 several really good models to look at, most
23 notably, I would like you to remember when you are
24 discussing the risk management what happened with
25 Clozaril because when Clozaril first got on the

1 market with the drug for schizophrenia, they had a
2 very stringent distribution program, and they were
3 sued by 30 states, attorneys general, because the
4 laws in those states said that you could not
5 restrict the distribution. In the settlement of
6 that case, the federal court assigned us, NORD,
7 with the task of distributing the drug to the
8 people in this class action settlement.

9 So, I am very sensitive to what happens.
10 FDA approved Clozaril's distribution program but
11 then the law said that they couldn't do it. So,
12 people really want the freedom to be able to get
13 the drug when they want it, when their doctor
14 prescribes it.

15 The other program you should look at is
16 thalidomide because it is an extraordinarily
17 important drug, again very orphan. Nobody wanted
18 to go near it because of the liability problem.
19 But they have a wonderful distribution program and
20 I think it should be a good model for the field
21 when there are drugs with specific dangers
22 involved.

23 I also want to give you several cautions.
24 Don't make the distribution too restrictive. For
25 example, don't allow just certain specialists to

1 prescribe it because people with narcolepsy have a
2 great deal of travel problems. Many of them don't
3 have driver's licenses in many states. They may
4 hold on to their driver's license but actually if
5 it was ever reported to the state that they had
6 narcolepsy they would lose it. It is just like
7 epilepsy. So, you have to be sensitive to that.

8 There are many current problems with
9 Ritalin and Dexedrine and the amphetamines that
10 they are using because the government limits the
11 amount of manufacture every year. So, at the end
12 of the year they run out of drug and there are
13 times when they just aren't able to fill their
14 prescriptions and they can't order it by mail order
15 because it is a controlled substance. So, these
16 people have suffered so tremendously because of
17 these distribution problems. With those drugs,
18 pharmacies don't stock a sufficient amount and they
19 will only dispense one month at a time.

20 Don't require a distribution program that
21 is going to cause legal problems. So, ask yourself
22 that, whether the program that has been designed by
23 Orphan Medical could be loosened up a bit.

24 The other thing goes back to what you were
25 talking about this morning, labeling. You know,

1 does this drug help with daytime sleepiness, etc.?
2 I want to caution you that if you label this drug
3 just for cataplexy with no effect on daytime
4 sleepiness, there are a lot of insurance companies
5 that are not going to reimburse for it. So,
6 labeling on a drug is extraordinarily important to
7 patients because of the managed care insurance
8 system. So, try to be as liberal as you can on
9 that, thinking about whether insurance companies
10 are going to say no, except to just people with a
11 particular type of narcolepsy.

12 Also, recognize that it is a unique
13 disorder that is just as crippling as epilepsy, and
14 that these people are already paying a very heavy
15 price because of the problems they have with their
16 current drugs.

17 Illegal use has to be handled, which I
18 know that you are going to do, but you must pay
19 attention to the valid use of this drug. Thank
20 you.

21 DR. KAWAS: Thank you, Ms. Meyers. You
22 are the first one who hasn't used all of your time
23 and that is greatly appreciated. The next one is
24 Robert L. Cloud, from the Narcolepsy Network.

25 MR. CLOUD: Good afternoon, and I wish to